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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,146	05/05/2006	Shyam S. Mohapatra	USF.T193XC1	9945

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,146	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/5/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,45,46 and 51-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45,46 and 51-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/5/09 has been entered.

Claims 64-68 were added by amendment on 3/5/09.

Claims 42, 45, 46, and 51-68 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 45, 46, and 51-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting expression of Dengue virus (DV) genes in a mouse animal model of DV infection by administering to the liver of the model a vector that expresses siRNA that reduces expression of a target DV gene by RNA interference, does not reasonably provide enablement for inhibiting expression of Dengue virus (DV) genes in a human by any route of administration, or in an animal model by intramuscular, subcutaneous, intradermal, oral, or nasal

administration, of a vector that expresses siRNA that reduces expression of a target DV gene by RNA interference. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting expression of Dengue virus (DV) genes within a mammalian animal host by administration to the host of a vector that expresses siRNA that reduces expression of a target DV gene in the host by RNA interference. This clearly requires delivery of the vector to cells that have been, or will be, infected by DV.

Adelman (2001, 2002, of record) taught that thoracic administration of antisense or siRNA expression vectors in mosquitoes allowed inhibition of DV replication in salivary glands. However, these teachings do not provide enablement for siRNA vector delivery and subsequent inhibition of DV replication in mammals due to the vast differences in size and complexity between the two classes of organisms. Administration to a mosquito is essentially equivalent to local administration to a small, restricted area of a mammal. Further guidance as to how to achieve delivery of an siRNA vector to the appropriate target cells would be required in order to enable the scope of the claimed invention embracing delivery to cells in an mammal in vivo.

Guidance in the specification as to how to achieve delivery to DV target cells is general. For example, the specification at paragraph 50 indicates that the "vectors of the present invention can be administered to a subject by any route that results in delivery of the genetic material (e.g., polynucleotides) and transcription of the

polynucleotides of the gene suppressor cassettes into siRNA molecules. The vectors of the present invention can be administered to a host "intravenously (I.V.), intramuscularly (I.M.), subcutaneously (S.C.), intradermally (I.D.), orally, intranasally, etc."

The specification at pages 29 and 30 teaches that resident skin dendritic cells (DC) are regarded as the targets for Dengue virus (DV) infection in mammals (citing Marovich (2001) and Wu (2000), of record)). Each of these papers shows that DV will infect DC in vitro, and provides evidence that DC cells present at a site of infection in vivo stained positively for a DV antigen (see e.g. Marovich at paragraph bridging pages 222 and 223, and Fig 5 on pg 223). However, those of skill in the art appreciate that positive staining of phagocytic cells such as DC does not provide proof of infection of DC in vivo. Jessie et al (J. Inf. Dis. 189: 1411-1418, 2004) at page 1411, paragraph bridging columns 1 and 2, taught that "the mere presence of viral antigens within cells does not necessarily mean that the cells in question support viral replication, since antigens may represent phagocytized, killed virus or sequestered immune complexes in the process of being degraded." Jessie further stated that "[e]vidence from in vitro studies suggested that other cells (e.g., hepatocytes, B and T lymphocytes, endothelial cells, and fibroblasts) could be potential targets for virus infection and replication, but relatively little is known about the involvement of these cells in in vivo infections [12 citations omitted]." Wu indicated that the initial target cell for DV infection had not yet been identified (first sentence of introduction on page 816), and the work of Wu and Marovich does not provide such an identification in view of the later teachings of Jessie. In summary, at the time of the invention, in vivo targets for DV infection and replication

had not yet been convincingly identified by those of skill in the art, and the specification fails to provide further evidence for identification of a target. Thus one of skill in the art relying on the teachings of the specification and the prior art would not know to which cells in a mammal an siRNA vector should be delivered.

Further, after the time of filing, Halstead (Vaccine 23: 849-856, 2005) reviewed the available knowledge regarding the relevant human cells in Dengue virus infection. Halstead indicated that DC can bind and take up DV through receptors known as DC-SIGN, and that evidence from human autopsies points to human monocyte/macrophages as prime targets supporting dengue virus replication in vivo. See pages 854 and 855. However, the studies providing this information did not provide sufficient evidence to conclude that these cells were in fact targets for DV infection and replication in vivo. Halstead concluded the review by stating that "[c]ritically missing in receptor research is the identity of the specific cells that support Dengue infections in human beings." Page 855, last paragraph. Thus the accumulated research was not sufficient as of 2005 to indicate to one of skill in the art that the targets for Dengue infection in humans had been identified.

It was also apparent from the teachings of the prior art that delivery of gene expression vectors in vivo, and obtaining appropriate expression therefrom, was problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated

further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3).

Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph.

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…". (pg. 581).

In summary, it is clear that in vivo gene delivery and expression is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems.

The specification provides no working example of the claimed invention.

Because the target cells for DV infection were not known at the time of the invention, the specification provides only general guidance as to how to deliver the required expression vector, the state of the art regarding therapeutic gene expression in vivo shows a high level of unpredictability, and the specification lacks a working example, one of skill in the art could not deliver the required expression vector to the appropriate cells in a mammalian host to inhibit expression of Dengue Virus genes without undue experimentation.

Response to Arguments

Applicant's arguments filed 3/5/09 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 5-8 of the response. Applicant submitted Tassaneetrithrep (2003), Seem and Jain (2005), and Halstead, 2005) in support of the view that Dendritic cells and macrophage monocytes are targets for DV infection in vivo. Tassaneetrithrep shows that DV can bind to DC in vitro via the receptor DC-SIGN, but indicates that limited data are available to establish the major sites of DV replication in vivo (page 823, right column). Tassaneetrithrep posits that DC-SIGN is a logical candidate for interrupting DV infection in humans, but does not provide any conclusive evidence that DV infects or replicates in DC in vivo. Tassaneetrithrep also indicates that DCs and not monocytes or macrophages are preferentially infected with DV (sentence bridging pages 823 and 824.) Seema and Jain indicated after the time of filing that monocyte macrophages are the principle target for DV (page 95, right column). However, no in vivo data is disclosed to support this statement. As discussed above, Halstead (2005) reviewed the state of the art, considered the in vitro infection data, and concluded that the identity of the specific cells that support Dengue infections in human beings was unknown. In view of the evidence of record, taken as a whole, it is clear that those of skill in the art did not know, at the time of the invention what were the targets for DV infection, and administration of DV siRNA.

Applicant also submitted a variety of publications regarding the state of the art of in vivo expression vector delivery. However, none of these references identifies the target cells to which siRNA should be delivered to inhibit DV gene expression, or explains how to deliver vectors to those cells. Applicant asserts that Agrawal (2003)

and Milhavet (2003) showed that many laboratories have had significant success with a variety of RNAi techniques and delivery methods. Applicant refers to Table 1 of Milhavet, which refers to a single example of vector-driven shRNA delivery in vivo in a mouse model. Only two of the 60 or so other examples in the Table are in vivo, and these do not rely on expression vectors. At least one of them relies on the high pressure tail vein injection method cited in the obviousness rejection below. This method is not suitable for use in humans. Accordingly, Milhavet does not provide evidence of enablement for the scope of inhibiting Dengue virus expression in humans. Applicant did not point to any specific support for in vivo use of siRNA expression vectors in Agrawal.

Applicant also asserts that RNAi-mediated silencing in vivo was demonstrated before and after the time of filing, citing Tolentino (2004) and Zimmerman (2006). The Tolentino reference discloses local delivery of siRNA in the eye. Absent evidence that the eye comprises target cells for Dengue virus infection, this reference has no relevance. The Zimmerman reference was published 2 years after the effective filing date of the instant application, and is not dispositive of the state of the art at the time of the invention. It also fails to identify target cells for DV infection.

Applicant asserts that the Examiner has not indicated what information or guidance is allegedly missing in the disclosure or prior art. This is incorrect. The Examiner clearly indicated that one of skill would not know to which cells the siRNA expression polynucleotide should be delivered, or how to deliver it to cells in which Dengue virus resides in vivo in an organism other than a disease model. The

Examiner further indicated that gene delivery and expression presented problems that need to be overcome to enable the invention as claimed. This contention is supported by the Coburn (J. Antimicro. Chemo. 51: 753-756, 2003) reference, submitted by Applicant on 3/5/09. Coburn states that "[o]ne impediment to utilizing RNAi technology for therapeutic benefit in humans remains the development of efficient delivery systems for siRNAs." Despite evident advances in expression technology, Coburn still indicates that "[c]learly, the objectives, in the short term, are to improve viral delivery systems with the goal of maximizing expression". Coburn concludes that the next few years of research will indicate whether RNAi technology will realize its potential as 'the next wave of therapeutic molecules'. See page 754. Lieberman (Trends Mol. Med 9(9): 397-403, 2003) submitted by Applicant on 3/5/09, stated that vector-mediated siRNA delivery had all of the advantages and drawbacks of gene therapy, wherein the drawbacks include "low proportion of transduced cells, rapid loss of gene expression, danger of oncogenic transformation from insertional mutagenesis" (see page 400, right column, last sentence of first full paragraph). These references provide further support for the position that expression vector-mediated therapy, as embraced by the instant claims, was not enabled at the time the invention was filed.

Applicant asserts that the in vitro examples given by the specification provide a reasonable correlation between the scope of the claims and the scope of enablement. This is unpersuasive because those of skill in the art at, and after, the time of the invention did not know what the in vivo targets for DV infection were, and the state of the art of vector-mediated gene therapy was highly unpredictable due to problems with

gene delivery and expression (as evidenced by Verma (1997), Anderson (1998), Somia and Verma (2000), Rosenberg (2000), and Caplen (2003), Coburn (2003), and Lieberman (2003) above. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42, 45, 46, 52, 53, 55, 58-60, 64, 65, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995), An et al (Virology 263: 70-77, 1999), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), Yu et al (PNAS 99(9): 6047-6052, 2002), and Liu et al (Gene Therapy 6 : 1258-1266, 1999).

The invention is a method for inhibiting the expression of Dengue virus genes within a mammalian animal host comprising administering to the host an expression vector comprising a polynucleotide encoding an siRNA that reduces expression of a target Dengue virus gene by RNA interference.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the portion of the RNA encoding the structural proteins, and the 3' end of the virus genome. Cells were exposed to DV after delivery of antisense. The target regions were 15 bases

in length. One oligonucleotide was directed to a target sequence common to all four DV serotypes. See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Raviprakash did not teach a vector encoding siRNA against DV RNA or administration to a mammalian animal host.

An taught a mouse animal model for DV infection. Human HepG2 cells, which support DV infection in vitro were transplanted into the spleen of SCID mice. The cells subsequently migrated to the liver, engrafted and grew there. Seven to eight weeks after transplantation, the mice were injected intraperitoneally with dengue virus type 2. The results indicated that the virus replicated in the Hep G2 cells. See abstract and Discussion.

Liu taught an efficient method for delivery of nucleic acids to the liver of mice by hydrodynamic tail vein injection. See abstract, and Fig. 2. Note that this technique is not suitable for use in humans.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus prM RNA, and its use to inhibit DV infection. See abstract. Adelman indicated that expression from a Sindbis vector of RNA with antisense polarity and that of RNA with sense polarity were equally effective to induce resistance to DEN-2 in mosquito cells and adult mosquitoes, noting that virus resistance had many of the characteristics of RNA silencing, including the presence of Dengue virus-specific siRNA.

Tuschl stated that “siRNAs are extraordinarily powerful reagents for mediating gene silencing” and that “siRNAs are effective at concentrations that are several orders

of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in and viral vectors. See last paragraph on page 6052

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Raviprakash by substituting for the antisense oligonucleotides a vector encoding one or more siRNAs. One would have been motivated to do so because Tuschl taught that siRNAs were more efficient than antisense. One would have had a reasonable expectation of success in view of the teachings of Yu, who showed that siRNA hairpin expression cassettes functioned in mammalian cells. In so doing, one would have been motivated to use any of the target sequences disclosed by Raviprakash or Adelman. One would have been motivated to include expression cassettes for more than one siRNA in order to increase the level of inhibition achieved.

It would have been similarly obvious to administer the vector discussed above to the animal model of An, using the method of Liu. One would have been motivated to do so in order to investigate the efficacy of the vectors in an animal model of the disease. One would have had a reasonable expectation of success in view of the results of Liu in delivering to the liver.

It is noted that the combined references are silent as to whether or not the siRNA vector is administered prior to or after DV administration. However, it would have been

obvious to perform the experiment in either order in order to simulate prophylactic and therapeutic modalities. Furthermore, MPEP 2144.04 states that the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

Claim 54 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995), An et al (Virology 263: 70-77, 1999), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), Yu et al (PNAS 99(9): 6047-6052, 2002), and Liu et al (Gene Therapy 6 : 1258-1266, 1999) as applied to claims 42, 45, 46, 52, 53, 55, 58-60, 64, 65, and 68 above, and further in view of Adelman et al (Insect Mol. Biol. 10(3): 265-273, 2001).

The teachings of Raviprakash, An, Adelman (2002), Tuschl, Yu, and Liu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a mammalian animal by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach siRNA directed against a non-structural gene.

Adelman (2001) showed that antisense directed against DV NS5 prevented DV replication. See last sentence of page 266 (referring to D1GDDAs and D3GDDAs); Fig. 1C on page 267 which shows that D1GDDAs and D3GDDAs are antisense sequences directed against NS5; and Table 1 on page 268 which shows that D1GDDAs and D3GDDAs inhibited DV replication.

It would been obvious to one of ordinary skill in the art at the time of the invention to target NS5 with an siRNA because Adelman (2001) showed that DV replication could be inhibited by antisense against NS5, and because Tuschl taught that siRNAs were more efficient than antisense.

Claim 57 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995), An et al (Virology 263: 70-77, 1999), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), Yu et al (PNAS 99(9): 6047-6052, 2002), and Liu et al (Gene Therapy 6 : 1258-1266, 1999) as applied to claims 42, 45, 46, 52, 53, 55, 58-60, 64, 65, and 68 above, and further in view of Yu et al (US 6852528).

The teachings of Raviprakash, An, Adelman (2002), Tuschl, Yu, and Liu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a mammalian animal by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach a vector conjugated with chitosan.

However, one of ordinary skill appreciates that there is a wide variety of gene delivery techniques which one may employ interchangeably as a matter of design choice. Among these are microinjection (the method used by Raviprakash), lipofection (used by Adelman (2002) and Yu (2002). Yu ('528) also taught that a variety of methods could be used to deliver nucleic acids to cells including microparticle formation with polycations such as chitosan-based compounds, as well as liposome-mediated

transfection and microinjection. See column 22, lines 17-44; column 23, lines 30-47; and column 31, lines 22-38. It would have been obvious to one of ordinary skill in the art to select any of these commonly used transfection techniques, as they were all well recognized in the art as exchangeable alternatives.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995), An et al (Virology 263: 70-77, 1999), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), Yu et al (PNAS 99(9): 6047-6052, 2002), and Liu et al (Gene Therapy 6 : 1258-1266, 1999) as applied to claims 42, 45, 46, 52, 53, 55, 58-60, 64, 65, and 68 above, and further in view of Kumar et al (US 7067633).

The teachings of Raviprakash, An, Adelman (2002), Tuschl, Yu, and Liu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a mammalian animal by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach a vector comprising a tissue-specific or inducible promoter.

One of ordinary skill in the art recognizes that particular promoters are selected as a matter of design choice. Inducible and tissue-specific promoters allow one to control the expression of a given construct either through the type of cell used or through the presence or absence of an inducer. For example, Kumar taught that it is important to employ a promoter and/or enhancer that effectively directs the expression

of the DNA segment in the cell type, organelle, and organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters enhancers, and cell type combinations for protein expression. Various promoters employed may be constitutive, tissue specific, inducible and/or useful under the appropriate conditions to direct high level expression of the introduced DNA segment. It would have been obvious to one of ordinary skill in the art to select any of these commonly used promoters based on the need to control expression as a matter of design choice.

Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995), An et al (Virology 263: 70-77, 1999), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), Yu et al (PNAS 99(9): 6047-6052, 2002), and Liu et al (Gene Therapy 6 : 1258-1266, 1999) as applied to claims 42, 45, 46, 52, 53, 55, 58-60, 64, 65, and 68 above, and further in view of Hope et al (US Patent 6,136,597)

The teachings of Raviprakash, An, Adelman (2002), Tuschl, Yu, and Liu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a mammalian animal by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

The cited references did not teach adeno-associated virus vectors.

Hope taught expression cassettes designed for delivery to the liver. Hope taught the cassettes could be delivered by a variety of viral or non-viral vectors, including

plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above, and to deliver it to the liver of the animal model of An.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official

central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635